

ABSTRACT OF THE INVENTION

The invention provides an automated method for identifying an optimal or near optimal mathematical model to describe observed data including a) the definition of a candidate model search space, b) methods for searching said candidate model search space to identify the optimal or near optimal model within said candidate model search space. The present invention includes algorithms for writing the computer code needed to implement and evaluate candidate models in the software package NONMEM.

-
- ⁱ Hanson KR, Ling R, Havir E. A computer program for fitting data to the Michaelis-Menten equation. *Biochemical & Biophysical Research Communications*. 29(2):194-7, 1967 Oct 26
- ⁱⁱ Krzyzanski W, Jusko WJ. Mathematical formalism for the properties of four basic models of indirect pharmacodynamic responses. *Journal of Pharmacokinetics & Biopharmaceutics*. 25(1):107-23, 1997 Feb.
- ⁱⁱⁱ *Applied Regression and Analysis*. Draper, NR, Smith H., John Wiley & Sons, Inc., New York, 1966
- ^{iv} Guidance for Industry, Population pharmacokinetics, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation. Feb 1999
- ^v Sheiner, LB. Analysis of Pharmacokinetic data using parametric models – 1: Regression models. *J Pharmacokinetics and Biopharmaceutics*. 1984;12(1), 93-118
- ^{vi} Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic--pharmacodynamic models. I. Models for covariate effects. *Journal of Pharmacokinetics & Biopharmaceutics*. 20(5):511-28, 1992 Oct.
- ^{vii} Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic--pharmacodynamic models. Advanced topics in Pharmacokinetic Pharmacodynamic modeling, 1995, Biomedical Simulation Resource. Editor D D'Argenio.
- ^{viii} Akaike A. Posterior probability for choosing a regression model. *Annals of the Institute of Mathematical Statistics*. 30: A9-14
- ^{ix} Ludden TM, Beal SL, Sheiner, LB. Comparison of the Akaike Information Criterion, the Schwarz criterion and the F test as guides to model selection.
- ^x Maitre PO, Buhner M, Thomson D, Stanski DR. A three-step approach combining Bayesian regression and NONMEM population analysis: application to midazolam. *Journal of Pharmacokinetics & Biopharmaceutics*. 19(4):377-84, 1991 Aug.
- ^{xi} Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM, *Pharmaceutical Research*. 15(9) 1463-8 Sep 1998
- ^{xii} Wade JR, Beal SL, Sambol NC. Interaction between Structural, statistical and covariate models in population pharmacokinetic analysis. *J Pharmacokinetics and Biopharmaceutics*. 1994 Vol 22, (2), 165-177
- ^{xiii} *Genetic algorithms in optimization and machine learning*. David Goldberg, Addison-Wesley Publishing Company Inc. 1989.
- ^{xiv} Glover, F. (1997). "A Template for Scatter Search and Path Relinking," in *Lecture Notes in Computer Science*, 1363, J.K. Hao, E. Lutton, E. Ronald, M. Schoenauer, D. Snyers (Eds.), pp. 13-54.
- ^{xv} Glover, F. and M. Laguna (1997). *Tabu Search*, Kluwer Academic Publishers.
- ^{xvi} Glover, F. (1977). "Heuristics for Integer Programming Using Surrogate Constraints," *Decision Sciences*, Vol 8, No 1, 156-166.
- ^{xvii} *Modern Heuristic Techniques for Combinatorial Problems* Glover, F. and M. Laguna Tabu search. C.R. Reeves (ed. Blackwell, Oxford, 70 - 150) 1993
- ^{xviii} Metropolis N, Rosenbluth A, Rosenbluth M, Teller A, Teller E. 1953 *Journal of Chemical Physics*. Vol 21, pp. 1087-1092

^{xix} *Parallel Problem Solving from Nature, PPSN IV* (editors Voigt H.-M, Ebeling W., Rechenberg I. and Schwefel H.-P) Darwen P. and Yao X (398-407) 1996

^{xx} NONMEM users guide, Part IV, NMTRAN Guide, Oct 1990. Boeckmann A, Beal S, Sheiner L.

Copyright by the Regents of the University of California.

^{xxi} NONMEM users guide, Boeckmann A, Beal S, Sheiner L. Copyright by the Regents of the University of California.